REMARKS

Claims 1-22, 24-36, and 51-80 are pending in the application. Claims 1, 8, 15, 52, 58, and 72 have been amended. Support for these amendments can be found in original claim 1 and in the specification at, e.g., page 7, lines 9-17, and page 15, lines 28-32. The specification has been amended to update the priority information and to remove browser-executable code. These amendments add no new matter.

Priority

Page 3 of the Office Action attributed a priority date of March 11, 1999 to the examined claims. Applicants respectfully submit that claims directed to a microparticle containing a polymeric matrix, a lipid, and a nucleic acid molecule are entitled to a priority date of at least January 22, 1998. However, irrespective of the priority date assigned to the claims, applicants submit that, in view of the amendments and remarks contained herein, the claims are patentable over all of the cited references.

The Response to Office Action filed on July 30, 2003 contained an amendment that inserted on the first page of the specification a reference to all prior applications. The first page of the specification has been updated by the present amendment to include the current status of all of the prior applications.

Specification

At page 4 of the Office Action, the specification was objected to as containing browser-executable code at page 5, line 18. The specification has been amended to remove the browser-executable code.

Claim Objections

At page 4 of the Office Action, claim 8 was objected to in its recitation of the term "at least" following the term "consisting of." The claim has been amended to recite

"comprising" in place of "consisting of."

At page 4 of the Office Action, claim 8 was objected to in its recitation of the phrase "sharing an overlapping sequence." The claim has been amended to recite "generated from an overlapping sequence" in place of "sharing an overlapping sequence."

It is applicants' understanding that the amendments to claim 8 overcome the foregoing objections.

35 U.S.C. §112, First Paragraph

At page 5 of the Office Action, claims 1-16, 18-21, 26, 33-36, and 51-80 were rejected as allegedly containing new matter. Independent claims 1, 8, 52, and 72 have been amended to contain a limitation that the microparticle is not encapsulated in a liposome. Support for this amendment can be found in original claim 1 and in the specification at, e.g., page 15, lines 28-32.

At pages 5-6 of the Office Action, claims 60 and 61 were rejected as allegedly containing new matter. Applicants respectfully submit that claims 60 and 61 are fully supported in the application as filed. For example, the specification discloses at, e.g., page 7, lines 18-21 and at page 20, lines 21-23 that a microparticle can contain a carbohydrate.

In view of the amendments to claims 1, 8, 52, and 72 and the foregoing remarks, applicants request that the Examiner withdraw the rejections.

35 U.S.C. §112, Second Paragraph

At page 6 of the Office Action, claims 8 and 15 were rejected as allegedly indefinite in their recitation of the term "at least" following the term "consisting of." The claims have been amended to recite "comprising" in place of "consisting of."

At page 6 of the Office Action, claim 58 was rejected as allegedly indefinite in its recitation of the phrase "further comprising a second lipid." The claim has been amended to recite the phrase "wherein each of the microparticles comprises a second lipid."

In view of the amendments to claims 8, 15, and 58, applicants request that the Examiner withdraw the rejections.

35 U.S.C. §102(a)

At pages 7-8 of the Office Action, claims 1, 6, 7, 52-55, 65, 66, 70, and 75 were rejected as allegedly anticipated by Lambert et al. (1998) Biochimie 80:969-76 ("Lambert").

Amended independent claim 1 is directed to a microparticle that is less than about 20 microns in diameter and contains a polymeric matrix, a lipid, and a nucleic acid molecule, wherein the nucleic acid molecule is contained within the microparticle. Similarly, amended independent claim 52 is directed to a preparation comprising a plurality of microparticles, each of which comprises a polymeric matrix, a nucleic acid molecule, and a lipid, wherein the nucleic acid molecule is contained within the microparticle. Support for the requirement that the nucleic acid molecule be contained within the microparticle can be found throughout the present application. For example, the specification states at page 7, lines 9-17 that

> [t]he nucleic acid in the microparticles described herein can be either distributed throughout the microparticle, or can be in a small number of defined regions within the microparticle. Alternatively, the nucleic acid can be in the core of a hollow core microparticle. The microparticle preferably does not contain a cell (e.g., a bacterial cell), or a naturally occurring genome of a cell, such as a naturally occurring intact genome of a cell.

Lambert describes antisense oligonucleotides adsorbed onto the surface of preformed polyisobutylcyanoacrylate particles pre-coated with cetyltrimethylammonium bromide. Lambert does not describe a microparticle that contains a nucleic acid molecule *within* the microparticle, as is required by the amended claims. As a result, the reference does not anticipate any of

claims 1, 6, 7, 52-55, 65, 66, 70, and 75. Accordingly, applicants respectfully request that the Examiner withdraw the rejection.

35 U.S.C. §102(b)

At page 8 of the Office Action, claims 1, 6, 7, 52-55, 65, 66, 70, and 75 were rejected as allegedly anticipated by Balland (1996) NATO ASI Series 290:131-42.

Similar to the disclosure of Lambert described above, Balland describes the adsorption of oligonucleotides and cetyltrimethylammonium bromide onto the surface of preformed polyisohexylcyanoacrylate particles. Balland (also like Lambert) does not describe a microparticle that contains a nucleic acid molecule *within* the microparticle, as is required by the amended claims. As a result, the reference does not anticipate any of claims 1, 6, 7, 52-55, 65, 66, 70, and 75. Accordingly, applicants respectfully request that the Examiner withdraw the rejection.

35 U.S.C. §102(e)

At pages 9-10 of the Office Action, claims 1-9, 11, 13, 16, 18, 21, 26, 33, 34, 51-54, 56, 58, 59, 62, 64, 65, and 70-76 were rejected as allegedly anticipated by Papahadjopoulos et al., U.S. Patent No. 6,210,707 ("Papahadjopoulos").

As detailed above in response to the section 102 rejections, the claimed microparticles contain a polymeric matrix, a lipid, and a nucleic acid molecule, wherein the nucleic acid molecule is contained within the microparticle. Papahadjopoulos describes several different lipid-containing compositions, none of which anticipates the currently claimed invention.

Papahadjopoulos describes cationic lipid:DNA complexes ("CLDCs") that contain (1) hydrophilic polymer, (2) nucleic acid that has been condensed with organic polycations, and (3) hydrophilic polymer and nucleic acid that has been condensed with organic polycations (Papahadjopoulos at column 1, lines 18-24). Papahadjopoulos's CLDCs do not contain a polymeric matrix and a nucleic acid within a microparticle. As a result, none of the CLDCs disclosed by Papahadjopoulos anticipates the currently claimed invention.

Papahadjopoulos also describes "lipidic microparticles" attached to proteins (Papahadjopoulos at column 1, lines 29-38). Papahadjopoulos's "lipidic microparticles" include liposomes, which are expressly excluded from the claims. None of the "lipidic microparticles" of Papahadjopoulos contain a polymeric matrix and a nucleic acid molecule contained within the microparticle, wherein the microparticle is not encapsulated in a liposome, as is required by the currently claimed invention.

In view of the claim amendments and foregoing comments, Papahadjopoulos does not anticipate any of claims 1-9, 11, 13, 16, 18, 21, 26, 33, 34, 51-54, 56, 58, 59, 62, 64, 65, and 70-76. Accordingly, applicants respectfully request that the Examiner withdraw the rejection.

35 U.S.C. § 103(a)

At pages 11-12 of the Office Action, claims 1, 8, 12, 52, 57, 58, 72, and 77-80 were rejected as allegedly unpatentable over Papahadjopoulos in view of Debs et al., U.S. Patent No. 5,827,703 ("Debs"). According to the Examiner,

> Papahadjopoulos teaches that the lipids are phospholipids but does not teach that these phospholipids are specifically phosphotidylcholine or phosphatidylethanolamine.
>
> Debs et al teach methods for introducing genes into cells by complexing DNA to lipid carriers (see e.g. abstract). The lipidic carriers are preferably phosphotidylcholine and phosphatidylethanolamine as these are suitable compounds for repeated injection into mammalian hosts.

As detailed above in response to the anticipation rejection, Papahadjopoulos does not describe a microparticle that contains a polymeric matrix, a lipid, and a nucleic acid molecule, wherein the nucleic acid molecule is contained within the microparticle, and wherein the microparticle is not encapsulated in a liposome and the microparticle does not comprise a cell. Debs was cited in the present rejection as disclosing phosphotidylcholine and phosphatidylethanolamine as lipidic carriers (features of dependent claims 12, 57, and 77-80). However, because the combination of Papahadjopoulos and Debs does not render obvious the

microparticle of claim 1 or 8 or the preparation of microparticles of claim 52 or 72, it necessarily follows that those claims that further limit the claimed microparticles are, for at least the same reasons, also non-obvious in view of the cited references. As a result, applicants respectfully request that the Examiner withdraw the rejection of claims 1, 8, 12, 52, 57, 58, 72, and 77-80.

At pages 12-13 of the Office Action, claims 8, 10, 52, and 55 were rejected as allegedly unpatentable over Balland in view of Papahadjopoulos. According to the Examiner,

> [n]either [Balland nor Papahadjopoulos] teach a microparticle comprising CTAB and a nucleic acid comprising at least 7 amino acids identical to at least a fragment of a naturally occurring mammalian protein.
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to complex the expression cassettes taught by Papahadjopoulos et al with CTAB as taught by Balland et al because Papahadjopoulos et al teach that it is within the ordinary skill of the art to generate lipid microparticles comprising nucleic acid expressing polypeptides for delivery to mammals and because Balland et al teach that it is within the ordinary skill of the art to adsorb nucleic acids to CTAB and polymeric matrices for gene delivery.

As detailed above in response to the anticipation rejection, Balland does not describe a microparticle that contains a nucleic acid molecule within a microparticle, as is required by the claims. Instead, Balland describes the adsorption of oligonucleotides and CTAB onto the surface of preformed particles. Papahadjopoulos was cited in the present rejection as disclosing expression cassettes. However, because the combination of Balland and Papahadjopoulos does not render obvious a microparticle that contains a polymeric matrix, a lipid, and a nucleic acid molecule, wherein the nucleic acid molecule is contained within the microparticle, and wherein the microparticle is not encapsulated in a liposome and the microparticle does not comprise a cell, it necessarily follows that those claims that require specific expression cassettes are, for at least the same reasons, also non-obvious in view of the cited references. As a result, applicants respectfully request that the Examiner withdraw the rejection of claims 8, 10, 52, and 55.

At pages 13-14 of the Office Action, claims 8, 14, 15, 19, 20, and 34-36 were rejected as allegedly unpatentable over Papahadjopoulos in view of Fikes et al., U.S. Patent No. 6,534,482 ("Fikes"). According to the Examiner,

> Papahadjopoulos does not teach that the microparticles are designed to deliver arrayed peptides...
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the lipid microparticles taught by Papahadjopoulos et al to deliver the nucleic acid encoding immunogenic peptides such as those that bind to MHC I molecules as taught by Fikes et al because Papahadjopoulos et al teach that it is within the ordinary skill of the art to generate lipid microparticles, comprising nucleic acid encoding therapeutic compositions, for delivery to mammals and because Fikes et al teach that it is within the ordinary skill of the art to employ arrays of peptides in a plasmid expression vector for therapeutic purposes such as to elicit an immune response.

As detailed above in response to the anticipation rejection, Papahadjopoulos does not describe a microparticle that contains a polymeric matrix, a lipid, and a nucleic acid molecule, wherein the nucleic acid molecule is contained within the microparticle, and wherein the microparticle is not encapsulated in a liposome and the microparticle does not comprise a cell. Fikes was cited in the present rejection as disclosing nucleic acids encoding arrayed immunogenic peptides. However, because the combination of Papahadjopoulos and Fikes does not render obvious the microparticle of claim 8, it necessarily follows that those claims that require nucleic acids encoding arrayed immunogenic peptides are, for at least the same reasons, also non-obvious in view of the cited references. As a result, applicants respectfully request that the Examiner withdraw the rejection of claims 8, 14, 15, 19, 20, and 34-36.

At pages 14-16 of the Office Action, claims 52 and 63 were rejected as allegedly unpatentable over Papahadjopoulos in view of Hedley et al., U.S. Patent No. 5,783,567 ("Hedley") or Ando et al. (1999) J. Pharm. Sci. 88:126-30 ("Ando"). According to the Examiner,

> Papahadjopoulos does not teach that the microparticles comprises nucleic acids of which at least 50% are supercoiled.

> Hedley et al teach a preparation of microparticles made up of a polymeric matrix and nucleic acids of which at least 50% are supercoiled...
>
> Ando et al teach use of supercoiled DNA that is at least 85% supercoiled...

As detailed above in response to the anticipation rejection, Papahadjopoulos does not describe a microparticle that contains a polymeric matrix, a lipid, and a nucleic acid molecule, wherein the nucleic acid molecule is contained within the microparticle, and wherein the microparticle is not encapsulated in a liposome and the microparticle does not comprise a cell. Hedley and Ando were cited in the present rejection as disclosing nucleic acids of which at least 50% are supercoiled. However, because the combination of Papahadjopoulos, Hedley, and Ando does not render obvious the preparation of microparticles of claim 52, it necessarily follows that dependent claims requiring a minimum percentage of supercoiled nucleic acid are, for at least the same reasons, also non-obvious in view of the cited references. As a result, applicants respectfully request that the Examiner withdraw the rejection of claims 52 and 63.

At pages 16-17 of the Office Action, claims 52 and 66-69 were rejected as allegedly unpatentable over Papahadjopoulos in view of Cleek et al. (1997) J. Biomed. Materials Res. 35:525-30 ("Cleek") as evidenced by Manoharan et al., U.S. Published Application No. 2005/0153337 ("Manoharan"). According to the Examiner,

> Papahadjopoulos does not teach that the polymeric matrix is PLGA wherein the ratio of lactic acid to glycolic acid is in the range of 1:2 to about 4:1 or about 65:35 by weight...
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the PLGA particles as taught by Cleek et al in the lipid microparticles taught by Papahadjopoulos et al because Cleek et al teach that it is within the ordinary skill in the art to use PLGA to deliver nucleic acids to cells and because Papahadjopoulos et al teach that it is within the ordinary skill of the art to complex synthetic polymers, i.e. PLGA, to nucleic acid for stable delivery to cells.

As detailed above in response to the anticipation rejection, Papahadjopoulos does not describe a microparticle that contains a polymeric matrix, a lipid, and a nucleic acid molecule, wherein the nucleic acid molecule is contained within the microparticle, and wherein the microparticle is not encapsulated in a liposome and the microparticle does not comprise a cell. Cleek was cited in the present rejection as disclosing PLGA microparticles. However, because the combination of Papahadjopoulos and Cleek does not render obvious the preparation of microparticles of claim 52, it necessarily follows that dependent claims requiring specific polymers are, for at least the same reasons, also non-obvious in view of the cited references. As a result, applicants respectfully request that the Examiner withdraw the rejection of claims 52 and 66-69.

Conclusions

Enclosed is a Petition for Extension of Time and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney docket No. 08191-014002.

Respectfully submitted,

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